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Synthesis of New Heterocycles: Part XXVIII* — Syntheses of Condensed Imidazoles†

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Reaction of imino ethers IIa, IIb, VI, IX and methylmercapto compounds XIIa and XIIc with aminoacetal, followed by treatment with HCl affords imidazo[2,1-*c*][1,4]thiazine (IVa), imidazo[2,1-*d*][1,4]thiazepine (IVb), imidazo[2,1-*a*]pyrazine (VIII), imidazo[1,2-*a*]azepine (X), imidazo[1,2-*a*]imidazole (XIIIa) and imidazo[1,2-*a*]pyrimidine (XIIIb) respectively. IVa and IVb are oxidized by acetic acid-hydrogen peroxide to the sulphones Va and Vb respectively; while nitration of XIIIa and XIIIb gives the mononitro derivatives XIVa and XIVb. Treatment of 2-mercaptoimidazole with ethylene dibromide affords imidazo[2,1-*b*]thiazole (XVa), which is further nitrated to the nitro compound XVb and then oxidized to the sulphone XVI. Several alicylic ketones and N-substituted piperidones have been condensed with histamine to give 7-spirocyclic imidazo[4,5-*c*]pyridines (XVIIIa-j, XX and XXI). Histamine and histidine are converted to their 5-nitro derivatives XVIId and XXV respectively. Interaction of XVIId with aromatic aldehydes yields imidazo[1,5-*c*]pyrimidines (XXIIIa-g).

IN the course of our exercises in medicinal chemistry, we had occasion to synthesize a variety of condensed imidazoles which are reported in this paper. Many of these ring systems have been already described in the literature, but the examples that we present now are novel in that they have generally at least one unsubstituted carbon atom on the imidazole ring which could be the target of electrophilic reactions such as nitration, leading to biologically interesting molecules.

Condensed Imidazoles with 1,2-Attachment

The majority of the compounds were prepared by the following route wherein the imidazole ring was built on an existing cyclic framework.

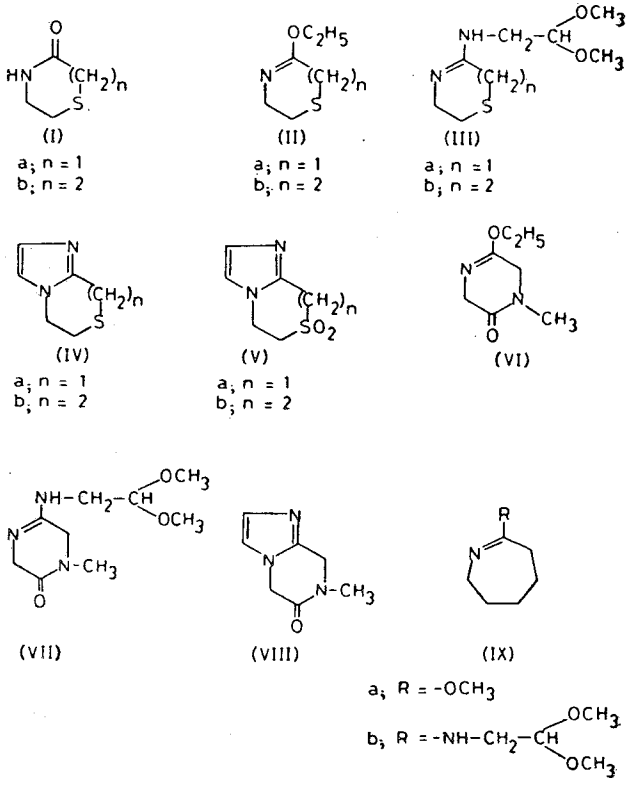
(a) *Imidazothiazine* (IVa) *and imidazothiazepine* (IVb) — Thiamorpholinone (Ia) was converted to the iminoether (IIa) by treatment with triethyl oxonium fluoborate. Reaction of IIa with aminoacetaldehyde dimethyl acetal furnished the amidine (IIIa) which underwent acid-catalysed ring closure to imidazothiazine (IVa) in 82% yield. The structure was supported by the appearance of a two-proton singlet at 7·50 in the NMR spectrum§ run in D_2O.

The synthesis of imidazothiazepine (IVb) followed a similar course starting from Ib and going through the imino ether (IIb) and amidine (IIIb). IVa and IVb were oxidized by hydrogen peroxide to the sulphones (Va) and (Vb) respectively.

(b) *Imidazopyrazine* (VIII) — This ring system was similarly constructed from the iminoether (VI) via the amidine (VII) which underwent acid-catalysed cyclodehydration to form VIII.

(c) *Imidazoazepine* (X) — Reaction of the iminoether (IXa) with aminoacetaldehyde dimethyl acetal afforded IXb which was cyclized to imidazoazepine (X) in 89% yield.

(d) *Imidazoimidazole* (XIIIa) *and imidazopyrimidine* (XIIIb) — Treatment of mercaptoimidazoline



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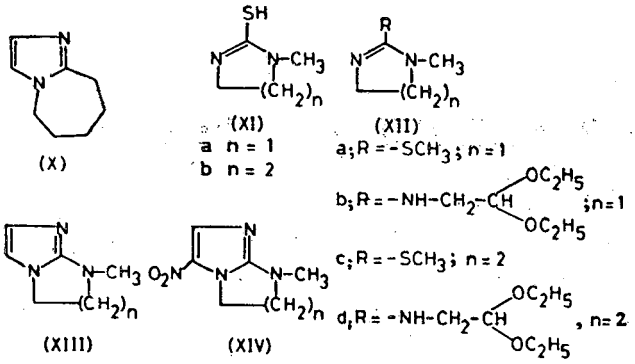
§NMR chemical shift in δ (ppm).



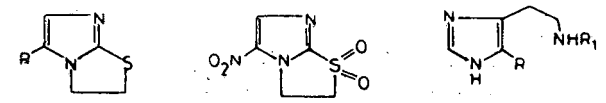
(X)

(XI)
a n = 1
b n = 2

(XII)
a; R = -SCH$_3$; n = 1
b; R = -NH-CH$_2$-CH(OC$_2$H$_5$)(OC$_2$H$_5$); n = 1
c; R = -SCH$_3$; n = 2
d; R = -NH-CH$_2$-CH(OC$_2$H$_5$)(OC$_2$H$_5$); n = 2

(XIII)
a; n = 1
b; n = 2

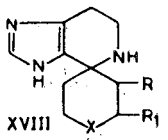
(XIV)
a; n = 1
b; n = 2



XV
a R = H
b R = NO$_2$

XVI

XVII
a R = R$_1$ = H
b R = H; R$_1$ = Ac
c R = NO$_2$; R$_1$ = Ac
d R = NO$_2$; R$_1$ = H

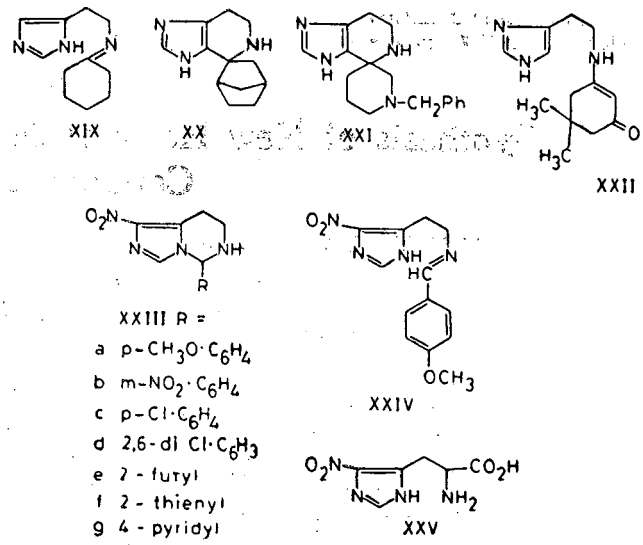


XVIII

	X	R	R$_1$
a	CH$_2$	H	H
b	CH$_2$	H	CH$_3$
c	CH$_2$	CH$_3$	H
d	CH(CH$_3$)	H	H
e	(CH$_2$)$_2$	H	H
f	(CH$_2$)$_7$	H	H
g	NCH$_3$	H	H
h	NCH$_2$Ph	H	H
i	NCOCH$_3$	H	H
j	NCOPh	H	H

(XIa) with methyl iodide yielded the methyl mercapto derivative (XIIa) which was converted to the guanidine (XIIb) and thence by acid into the imidazoimidazole (XIIIa) in 70% yield. The presence of an *AB* quartet in the NMR spectrum in $CDCl_3$ at 6·54 and 6·64 (J = 1·5 Hz) supported the structure of XIIIa. The synthesis of imidazopyrimidine (XIIIb) proceeded likewise from the mercaptotetrahydropyrimidine (XIb) via the S-methyl derivative (XIIc) and the guanidine (XIId). XIIIa and XIIIb were nitrated to give nitro-derivatives of presumed structures (XIVa) and (XIVb) respectively. In contrast, condensed imidazoles (IV), (VIII) and (X) could not be successfully nitrated, presumably due to insufficient activation of the imidazole nucleus.

(e) *Imidazothiazole* (XV) — Treatment of 2-mercaptoimidazole[1] with ethylenediamine under conditions somewhat different from those reported[2] gave XV in 83% yield. Nitration gave in low yield XVa which was further oxidized to the sulphone (XVI).



XIX XX XXI XXII

XXIII R =
a p-CH$_3$O·C$_6$H$_4$
b m-NO$_2$·C$_6$H$_4$
c p-Cl·C$_6$H$_4$
d 2,6-di Cl·C$_6$H$_3$
e 2-furyl
f 2-thienyl
g 4-pyridyl

XXIV

XXV

***Condensed Imidazoles with 4,5-Attachment — Imidazo[4,5-c]pyridines* (XVIII)**

This ring system is known to be formed by the condensation of histamine (XVII) with some aldehydes and ketones, but the reaction has not been widely studied. We were especially interested in the spirocyclic derivatives of structure (XVIII). XVIIIa has been prepared from XVII by condensation with histamine[3]. In our study, its structure was confirmed and the alternative possibility XIX ruled out by a study of the NMR spectrum which showed in the aromatic region a one-proton singlet at 7·40. XIX should show signals for two protons in the aromatic regions. Compounds XVIIIb-j, XX and XXI were synthesized similarly from histamine and appropriate ketones, in moderate to good yields. These are presented in Table 1. Cyclooctanone and camphor were unreactive towards histamine. In each case, the NMR spectrum exhibited one-proton singlet in the aromatic region between 7·35 and 7·45 as expected. From dimedone only the enaminoketone (XXII) was obtained and not a spirocyclic derivative. Attempts to introduce aryl azo group into the imidazole part of XVIII by coupling with aryl diazonium chloride[4] did not succeed. The azo group could be subsequently reduced to an amine which can then be oxidized to a nitro group.

***Condensed Imidazoles with 1,5-Attachment — Imidazo[1,5-c]pyrimidines* (XXIII)**

It was evident from our experience with imidazo-[4,5-*c*]pyridines that construction of imidazo[1,5-*c*]-pyrimidine ring system from histamine would require blocking position-5. Nitro group was an automatic choice for this approach in view of the known importance of nitroimidazoles in the field of antiprotozoals[5]. At the time this project was taken up, 5-nitrohistamine (XVIId) was unknown and we synthesized it by nitration of N-acetylhistamine (XVIIb) and hydrolysis of the resultant nitro-derivative (XVIIc). Subsequently XVIId has been revealed in a publication[6]. Nitrohistidine (XXV) was synthesized similarly from N-phthaloylhistidine methyl ester.

TABLE 1 — 7-SPIROCYCLIC-4,5,6,7-TETRAHYDROIMIDAZO[4,5-*c*]PYRIDINES

Compd	m.p. °C	Yield (%)	Crystallized from	Mol. formula	Calc. (%)			Found (%)		
					C	H	N	C	H	N
XVIIIa	217-19	75	Aq. EtOH	$C_{11}H_{17}N_3$	69·07	8·96	21·97	68·83	9·20	22·18
XVIIIa dinitrate	207-9	67	MeOH	$C_{11}H_{19}N_5O_6$	41·64	6·04	22·07	41·95	6·35	21·90
XVIIIb	222-23	—	EtOAc	$C_{12}H_{19}N_3$	70·20	9·33	20·47	70·31	9·50	20·13
XVIIIb dinitrate	214	47	MeOH	$C_{12}H_{21}N_5O_6$	43·50	6·39	21·14	43·54	6·54	21·50
XVIIIc dinitrate	205 (d)	20	MeOH-EtOH	$C_{12}H_{21}N_5O_6$	43·50	6·39	21·14	43·53	6·50	20·76
XVIIId	241-43	62	EtOAc	$C_{12}H_{19}N_3$	70·20	9·33	20·47	70·06	9·60	20·80
XVIIIe	214-15	30	Aq. EtOH	$C_{12}H_{19}N_3$ (M^+ 205)	70·20	9·33	20·47	70·01	9·57	20·45
XVIIIf trinitrate	214 (d)	36	EtOH	$C_{17}H_{31}N_5O_6$	43·96	6·94	18·10	74·24	7·23	19·56
XVIIIg	257-58	57	EtOH-EtOAc	$C_{11}H_{18}N_4$	64·04	8·80	27·16	64·25	8·88	27·04
XVIIIh	215-17	80	EtOH-Et_2O	$C_{17}H_{22}N_4$ (M^+ 282)	72·35	7·85	19·84	72·35	8·20	19·74
XVIIIi	239-41	—	EtOH-EtOAc	$C_{12}H_{18}N_4O$	61·51	7·74	23·91	61·03	7·93	23·17
XVIIIi dinitrate	220 (d)	67	MeOH	$C_{12}H_{20}N_6O_7$	40·00	5·59	23·33	40·13	5·76	23·67
XVIIIj	221-23	90	Aq. EtOH	$C_{17}H_{20}N_4O$	68·89	6·80	18·91	68·58	7·36	18·66
XX	210-12	3	H_2O	$C_{12}H_{17}N_3$ (M^+ 203)	70·90	8·43	20·67	70·22	8·83	20·53
XXI tri-HCl	252 (d)	83	MeOH-EtOH	$C_{17}H_{25}Cl_3N_4$	52·11	6·43	14·30	51·48	6·91	13·78

TABLE 2 — IMIDAZO[1,5-*c*]PYRIMIDINES (XXII)

Compd	m.p. °C	Yield (%)	Crystallized from	Mol. formula	Calc. (%)			Found (%)		
					C	H	N	C	H	N
XXIIa	203-4	91	Aq. EtOH	$C_{13}H_{14}N_4O_3$	56·93	5 15	20·43	57·18	5·71	20·33
XXIIb	230-33	76	DMF-EtOH	$C_{12}H_{11}N_5O_4$	49·83	3·83	24·21	49·99	4·12	24·11
XXIIc	200-2	65	EtOH	$C_{12}H_{11}ClN_4O_2$	51·73	3·98	20·10	52·02	4·24	20·31
XXIId	138-40	48	do	$C_{12}H_{10}Cl_2N_4O_2$	46·02	3·22	17·89	45·90	3·44	18·23
XXIIe	164-66	64	do	$C_{10}H_{10}N_4O_3$	51·28	4·30	23·92	51·40	4·62	23·78
XXIIf	182-83	66	do	$C_{10}H_{10}N_4O_2S$	48·00	4·02	22·39	48·09	4·14	22·13
XXIIg	220 (d)	55	do	$C_{11}H_{11}N_5O_2$	53·87	4·52	28·56	53·99	4·71	28·66

Reaction of 5-nitrohistamine (XVIId) with anisaldehyde gave the imidazopyrimidine (XXIIIa). Its NMR spectrum in DMSO-d_6 showed a singlet at 7·5 attributable to the nitroimidazole proton. The alternative structure XXIV would require the presence of an additional singlet at lower field due to the azomethine proton. XXIIIb-g were synthesized from XVIId by the use of other aldehydes. These are presented in Table 2. Cyclic products were not obtained from XVIId and formaldehyde or acetone. Nitrohistidine (XXV) did not also give cyclic products with aldehydes.

Experimental Procedure

All melting points are uncorrected. UV spectra (λ_{max} in nm) were determined in 95% ethanol; log ϵ values are given in parentheses. IR spectra (ν_{max} in cm^{-1}) were taken in nujol. NMR spectra were generally run in $CDCl_3$ solution on a Varian A60 spectrometer, using TMS as internal standard. Mass spectra were recorded on a Varian-Atlas CH-7 mass spectrometer at 70 eV ionizing beam using direct insertion probe.

5,6-*Dihydro*-3-*ethoxy*-2*H*-1,4-*thiazine* (IIa) — This imino ether was prepared from thiamorpholinone (Ia) and triethyl oxonium fluoborate by the method of Rajappa *et al.*[7]; b.p. 88-90°/5-7 mm, n_D^{29} 1·4783 (Found: C, 49·73; H, 7·67; N, 9·85. $C_6H_{11}NOS$ requires C, 49·64; H, 7·64; N, 9·65%).

4-*Ethoxy*-2,3,6,7-*tetrahydro*-1,4-*thiazepine* (IIb) — A solution of BF_3-etherate (114 g) in dry ether (500 ml) was added under anhydrous conditions, to a solution of epichlorohydrin (84 g) in dry ether (125 ml) at such a rate that ether just refluxed. The reaction mixture was stirred for 18 hr. A sticky mass was obtained, ether decanted, washed twice with dry ether by decantation. The residue was first dried *in vacuo* for 10 min.

The above Meerwein's reagent was dissolved in dry methylene chloride (350 ml) and added dropwise to a solution of the lactam (Ib) (65·5 g) in dry methylene chloride (250 ml). The reaction mixture was stirred overnight and treated with a solution of potassium carbonate (76 g) in water (150 ml). The organic layer was separated, dried (Na_2SO_4), the solvent was distilled off and the residue distilled to afford IIb, 25 g (36%), b.p. 75-80°/3 mm (Found: C, 52·59; H, 8·55; N, 9·03. $C_7H_{13}NOS$ requires C, 52·81; H, 8·55; N, 8·80%).

5,6-*Dihydro*-3-(2,2-*dimethoxyethylamino*)-2*H*-1,4-*thiazine* (IIIa) — A solution of aminoacetaldehyde dimethyl acetal hydrochloride (2·83 g) in absolute

ethanol (20 ml) was treated with IIa (2·9 g). The reaction mixture was stirred at room temperature for 72 hr. The solvent was distilled off and the residue recrystallized from isopropanol-ethyl acetate to afford IIIa, 4 g (82%), m.p. 133-34°; IR: 1610 (—N=C—), 3340 (—NH) (Found: C, 40·34; H, 7·45; N, 11·73. $C_8H_{16}N_2O_2S.HCl$ requires C, 39·92; H, 7·12; N, 11·64%).

4-(2,2- *Dimethoxyethylamino*)-2,3,6,7- *tetrahydro*-1,4-*thiazepine* (IIIb) — This compound was prepared from (IIb) (3·2 g) and aminoacetaldehyde dimethyl acetal hydrochloride (2·85 g) in the manner described for IIIa. The product was recrystallized from methanol-ethyl acetate to afford IIIb, 2·4 g (48%), m.p. 180-81° (Found: C, 42·70; H, 7·70; N, 11·29. $C_9H_{18}N_2O_2S.HCl$ requires C, 42·44; H, 7·52; N, 10·99%).

5,6-*Dihydro*-8*H*-*imidazo*[2,1-*c*][1,4]*thiazine* (IVa) — A solution of IIIa (26·6 g) in isopropanol (190 ml) was treated with 5*N* isopropanolic hydrogen chloride (38 ml). The reaction mixture was boiled under reflux for 5 hr, solvent distilled off and the residue recrystallized from methanol-ethyl acetate to afford IVa as hydrochloride, 17 g (85%), m.p. 229-30° (d); NMR (D_2O): 3·26 (*t*, 2H, $-CH_2$ at C-6), 4·18 (*s*, 2H, $-CH_2$ at C-8), 4·53 (*t*, 2H, $-CH_2$ at C-5), 7·50 (*s*, 2H, aromatic protons at C-2 and C-3) (Found: C, 41·01; H, 5·37; N, 15·89. $C_6H_8N_2S.HCl$ requires C, 40·80; H, 5·14; N, 15·86%).

5,6,8,9 - *Tetrahydro* - *imidazo*[2, 1- *d*][1, 4]*thiazepine* (IVb) — This compound was prepared from IIIb (11·4 g) and 5*N* isopropanolic HCl (20 ml) in isopropanol (100 ml) in the manner described for IVa. The product was recrystallized from isopropanol-ethyl acetate to afford IVb as hydrochloride, 5·3 g (62%), m.p. 233° (Found: C, 44·45; H, 6·16; N, 14·62. $C_7H_{10}N_2S.HCl$ requires C, 44·10; H, 5·82; N, 14·70%). The base liberated from the above hydrochloride was recrystallized from methylene chloride-*n*-hexane to afford IVb, m.p. 118-20° (Found: C, 54·64; H, 6·78; N, 18·43; M^+ 154. $C_7H_{10}N_2S$ requires C, 54·55; H, 6·54; N, 18·17%; mol. wt 154).

5,6-*Dihydro*-7,7-*dioxido*-8*H*-*imidazo*[2,1-*c*][1,4]*thiazine* (Va) — A suspension of IVa (8·85 g) in glacial acetic acid (25 ml) was treated dropwise with 30% (v/v) H_2O_2 (14 ml) at 15-20°. The reaction mixture was stirred overnight. The initial suspension gradually dissolved to give a clear solution. On continued stirring, a crystalline precipitate was formed. This was filtered and recrystallized from water to afford Va, m.p. 270° (d); IR: 1380 ($-SO_2-$) (Found: C, 34·15; H, 4·19; N, 12·97. $C_6H_8N_2O_2S.HCl$ requires C, 34·54; H, 4·35; N, 13·43%).

7,7- *Dioxido* - 5,6,8,9- *tetrahydro-imidazo*[2,1-*d*][1,4]-*thiazepine* (Vb) — This compound was prepared from IVb (4·8 g) and 30% (v/v) H_2O_2 (10 ml) in glacial acetic acid (8 ml) as described for Va. The product was recrystallized from aq. DMF to afford Vb, m.p. >300°; IR: 1378 ($-SO_2-$) (Found: C, 37·63; H, 5·23; N, 12·68. $C_7H_{10}N_2O_2S.HCl$ requires C, 37·76; H, 4·98; N, 12·58%).

3-(2′,2′-*Dimethoxyethylamino*)-5,6-*dihydro*-1-*methyl*-6-*oxo*-2*H*-*pyrazine* (VII) — A solution of 5,6-dihydro-3-ethoxy-1-methyl-6-oxo-2H-pyrazine (VIII) (5·5 g) in absolute ethanol (20 ml) was added dropwise to a solution of aminoacetaldehyde dimethyl acetal hydrochloride (5 g) in absolute ethanol (20 ml). The reaction mixture was stirred for 3 days under anhydrous conditions. The solvent was distilled off, and the residue recrystallized from methanol-ethyl acetate to afford VII, 7 g (63%), m.p. 156°; IR: 1680 (—C(=O)—N—CH_3), 3240 (—NH) (Found: C, 43·14; H, 7·49; N, 17·04. $C_9H_{17}N_3O_3.HCl$ requires C, 42·94; H, 7·21; N, 16·69%).

5,6- *Dihydro*-7-*methyl* -6-*oxo*-8*H*-*imidazo*[2,1-*a*]*pyrazine* (VIII) — This compound was prepared from VII (6·3 g) and 5*N* isopropanolic hydrogen chloride (13 ml) in isopropanol (65 ml) as described for IVa. The product was recrystallized from methanol-ethyl acetate to afford VIII as hydrochloride, 2·25 g (50%), m.p. 240-41°; IR: 1680 (—C(=O)—N—CH_3) (Found: C, 45·10; H, 5·35; N, 22·12. $C_7H_9N_3O.HCl$ requires C, 44·81; H, 5·37; N, 22·39%).

2-(2′,2′-*Dimethoxyethylamino*)-7*H*-3,4,5,6-*tetrahydro-azepine* (IXb) — This compound was prepared from O-methylcaprolactim (12·1 g) and aminoacetaldehyde dimethyl acetal hydrochloride (14·15 g) in absolute ethanol (80 ml) as described for IIIa. The product was recrystallized from methanol-ethyl acetate to afford IXb, 23 g (95%), m.p. 172-73° (Found: C, 51·04; H, 9·04; N, 11·94. $C_{10}H_{20}N_2O_2.HCl$ requires C, 50·73; H, 8·94; N, 11·83%).

9*H* -5,6,7,8- *Tetrahydroimidazo*[1,2-*a*]*azepine* (X) — This compound was prepared from IXb (21·3 g) and 5*N* isopropanolic hydrogen chloride (18 ml) in isopropanol (90 ml) as described for IVa. The product was recrystallized from isopropanol-ethyl acetate to afford X, 13 g (89%), m.p. 178° (Found: C, 55·22; H, 7·90; N, 16·29. $C_8H_{12}N_2.HCl$ requires C, 55·65; H, 7·59; N, 16·22%). (This compound was somewhat hygroscopic and anhydrous solvent is absolutely necessary for recrystallization.)

4,5 - *Dihydro* -2- *mercaptomethyl* -1- *methylimidazole* (XIIa) — A solution of 4,5-dihydro-2-mercapto-1-methyl imidazole (XIa) (23·2 g) in methanol (300 ml) was treated with methyl iodide (45 g). The reaction mixture was boiled under reflux for 1 hr. On cooling to 0°, a crystalline precipitate was formed. This was filtered and recrystallized from methanol-ethyl acetate to afford XIIa, 36 g (46%) as hydroiodide, m.p. 78-80° (Found: C, 23·24; H, 4·50; N, 10·78. $C_5H_{10}N_2S.HI$ requires C, 23·26; H, 4·30; N, 10·86%).

5,6 - *Dihydro* -7- *methyl*-7*H*- *imidazo*[1,2-*a*]*imidazole* (XIIIa) — A solution of XIIa (37 g) in isopropanol (100 ml) was treated with aminoacetaldehyde diethyl acetal (18·6 g). The reaction mixture was boiled under reflux for 15 hr. The solvent was distilled off; the crude hydroiodide of XIIb thus obtained was treated with conc. hydrochloric acid (30 ml) and heated at 100° for 1 hr. It was allowed to stand at room temperature overnight. The excess of hydrochloric acid was distilled off and residual gum

taken up in methanol (100 ml), rendered alkaline with 60% NaOH solution and extracted with methylene chloride. The organic extract was dried (Na_2SO_4), the solvent removed and the residue (18·5 g) chromatographed on a column of neutral alumina (500 g) using benzene as the solvent. That fraction which eluted with benzene, was distilled to afford XIIIa, 12·5 g (70%), b.p. 128°/0·5 mm; NMR: 2·79 (*s*, 3H, $>N-CH_3$), 3·50-4·00 (complex *m*, 4H, $-CH_2-$ at C-5 and C-6), 6·54 (*d*, 1H, aromatic proton), 6·64 (*d*, 1H, aromatic proton) (Found: C, 58·42; H, 7·32; N, 34·20. $C_6H_9N_3$ requires C, 58·51; H, 7·37; N, 34·12%).

4,5-*Dihydro*-2-*mercaptomethyl*-1-*methyl*-6*H*-*pyrimidine* (XIIc) — A solution of (XIb) (22 g) in methanol (200 ml) was treated with methyl iodide (27 g). The reaction mixture was boiled under reflux for 1 hr. On the addition of ether (500 ml) and cooling to 10°, a crystalline precipitate was formed. This was filtered and recrystallized from methanol-ether to afford XIIc as hydroiodide, 45 g (91%), m.p. 120° (Found: C, 26·64; H, 5·15; N, 10·49. $C_6H_{12}N_2S.HI$ requires C, 26·48; H, 4·82; N, 10·30%).

5,6,7,8 - *Tetrahydro* -8- *methyl-imidazo*[1,2-*a*]*pyrimidine* (XIIIb) — This compound was prepared from XIIc (46 g) and aminoacetaldehyde diethyl acetal (22·6 g) as described for XIIIa. The product was distilled *in vacuo* to afford XIIIb, 20·5 g (80%), b.p. 135-38°/0·5 mm; NMR: 1·98 (complex *m*, 2H, $-CH_2-$ at C-6), 2·92 (*s*, 3H, $>N-CH_3$), 3·06 (*m*, 2H, $-CH_2-$ at C-7), 3·67 (*t*, 2H, $-CH_2-$ at C-5), 6·38 (*d*, 1H, aromatic proton), 6·56 (*d*, 1H, aromatic proton) (Found: C, 61·25; H, 8·10; N, 30·65. $C_7H_{11}N_3$ requires C, 61·28; H, 8·08; N, 30·63%).

5,6-*Dihydro*-7-*methyl*-3-*nitro*-7*H*-*imidazo*[1,2-*a*]*imidazole* (XIVa) — A solution of XIIIa (12 g) in glacial acetic acid (35 ml) was treated dropwise with conc. HNO_3 (12 ml) at 0° during 1 hr. The reaction mixture was stirred for further 1 hr, neutralized carefully with conc. ammonia. A crystalline precipitate was obtained. This was filtered and recrystallized from methylene chloride-ether to afford XIVa, 2·1 g (12%), m.p. 164-65°; UV: 386 (4·03); IR: 1610 (aromatic); NMR: 3·02 (*s*, 3H, $>N-CH_3$), 3·94 (*m*, 2H, $-CH_2-$ at C-6), 4·35 (*m*, 2H, $-CH_2-$ at C-5), 7·70 (*s*, 1H, aromatic proton at C—2) (Found: C, 43·19; H, 5·15; N, 33·04; M^+ 168. $C_6H_8N_4O_2$ requires C, 42·85; H, 4·80; N, 33·30%; mol. wt 168).

5,6,7,8- *Tetrahydro* -8- *methyl* -3-*nitroimidazo*[1,2-*a*]-*pyrimidine* (XIVb) — This compound was prepared by nitration of (XIIIb) (17 g) in glacial acetic acid (50 ml) and conc. HNO_3 (17 ml) as described for XIVa. The product was recrystallized from methylene chloride-ether to afford XIVb, 1·5 g (8%), m.p. 149-51°; UV: 400 (4·16); IR: 1620 (aromatic); NMR: 2·20 (complex *m*, 2H, $-CH_2-$ at C-6), 3·18 (*s*, 3H, $-\underset{|}{N}-CH_3$), 3·31 (*m*, 2H, $-CH_2-$ at C-7), 4·30 (*t*, 2H, $-CH_2-$ at C-5), 7·85 (*s*, 1H, aromatic proton at C-2) (Found: C, 46·36; H, 5·81; N, 30·77; M^+ 182. $C_7H_{10}N_4O_2$ requires C, 46·15; H, 5·52; N, 30·76%; mol. wt 182).

2,3 - *Dihydroimidazo*[2,1- *b*]*thiazole* (XVa) — To a mixture of ethylene dibromide (20 ml), sodium carbonate (20 g) and isopropanol (100 ml) was added dropwise 2-mercaptoimidazole (5 g) in 20% aq. potassium hydroxide (20 ml) and isopropanol (50 ml). The mixture was stirred and heated under reflux for 4 hr. It was then cooled and filtered. The filtrate was concentrated *in vacuo* to a small volume and treated with 20% aq. potassium hydroxide (50 ml). The oil thus liberated was extracted with chloroform (3 × 60 ml). The chloroform extracts were dried and the solvent removed to give XVa (5·2 g) as an oil.

2,3-*Dihydro* -5-*nitroimidazo*[2,1-*b*]*thiazole* (XVb) — XVa (6 g) was added dropwise during 15 min into conc. nitric acid (15 ml) kept at 70-80° under nitrogen atmosphere. The solution was heated at the same temperature for a further period of 40 min, cooled and treated with saturated aq. sodium acetate to *p*H 6·5. The product was filtered off and crystallized from methanol to afford XVb (1·5 g), m.p. 142-43° (Found: C, 35·22; H, 3·12; N, 24·66. $C_5H_5N_3O_2S$ requires C, 35·09; H, 2,95; N, 24·56%); NMR (DMSO-d_6): 4·05 (SCH_2, 2H *t*), 4·62 (NCH_2, 2H, *t*), 7·97 (*s*, 1H, imidazole H); UV: 350 (3·98).

2,3-*Dihydro*-5-*nitroimidazo*[2,1-*b*]*thiazole*-1,1-*dioxide* (XVI) — A solution of XVb (1·8 g) in chloroform (100 ml) was added during 45 min to an ethereal solution of monoperphthalic acid (0·1 mole in 50 ml) with stirring and cooling at 0 to −4°. The solution was stirred for a further period of 2 hr at 0°, left overnight at room temperature and then refluxed gently for 2 hr. Phthalic acid separated and was filtered off. The filtrate was washed with saturated aq. sodium bicarbonate, dried and evaporated. The residue was crystallized from ethanol to give the sulphone (XVI) (1·2 g), m.p. 216-17° (Found: C, 29·76; H, 2·66; N, 20·91. $C_5H_5N_3O_4S$ requires C, 29·57; H, 2·48; N, 20·69%); NMR (DMSO-d_6) 4·25 (SCH_2, 2H, *t*), 4·95 (NCH_2, 2H, *t*), 8·25 (*s*, 1H, imidazole H); UV 288 (3·94).

7 - *Spirocyclic* - 4,5,6,7 - *tetrahydroimidazo*[4,5-*c*]*pyridines* (XVIII), (XX) *and* (XXI) — These were prepared by the following procedure used for XVIIIa. Data on the products are given in Table 1.

A solution of histamine dihydrochloride (2·76 g; 15 mmoles) in methanol (50 ml) was added to methanolic sodium methoxide (from 0·69 g sodium and 15 ml methanol). Sodium chloride was filtered and the methanol distilled off from the filtrate. To the residue was added cyclohexanone (1·48 g, 15 mmoles) and ethanol (50 ml) and the solution heated under reflux for 15 hr. Solvent was then evaporated off and the residual XVIIIa characterized as the free base and the nitrate salt.

When dimedone was used as the ketonic component, enaminoketone XXII resulted and was recrystallized from ethanol-ether; 35%, m.p. 183-85° (Found: C, 66·88; H, 8·46; N, 17·72. $C_{13}H_{19}N_3O$ requires C, 66·92; H, 8·21; N, 18·01%); NMR (DMSO-d_6): 4·95 (*s*, 1H, $H-\underset{|}{N}=$).

5 - *Nitrohistamine* (XVIId) — N - Acetylhistamine (XVIIb) was converted to the nitrate salt, m.p.

170°. The nitrate salt (6 g) was added to conc. sulphuric acid (18 ml) and the solution heated on a steam-bath for 2 hr. It was then poured into ice-cold water and made basic with conc. aq. ammonia. XVIIc was precipitated, filtered and recrystallized from methanol, 5 g, m.p. 236-38° (Found: C, 42·38; H, 5·39; N, 28·38. $C_7H_{10}N_4O_3$ requires C, 42·42; H, 5·09; N, 28·27%).

XVIIc (15 g) and 6*N* HCl (750 ml) were heated under reflux for 4 hr. The solution was evaporated *in vacuo* to dryness. Addition of ethanol gave XVIId as the crystalline HCl salt. This was filtered off and recrystallized from aq. ethanol; 13·7 g, m.p. 275-79° (d) (Found: C, 31·57; H, 4·97; N, 29·23. $C_5H_9ClN_4O_2$ requires C, 31·18; H, 4·71; N, 29·09%); NMR (D_2O): 3·40 (*s*, 4H, $-CH_2-CH_2-$), 7·67 (*s*, 1H, C-2H).

Imidazo[1,5-*c*]*pyrimidines* (XXIIIa-j)— These were prepared by the following general procedure. Details are given in Table 2.

A solution of nitrohistamine HCl (0·97 g, 5 mmoles) in water (2 ml) was treated with shaking with thiophene-2-aldehyde (0·56 g, 5 mmoles) and sodium hydroxide (0·22 g, 5·5 mmoles) in water (2 ml). The crystalline product was filtered and recrystallized from ethanol.

5 - *Nitrohistidine* (XXV) — N - Phthalolylhistidine methyl ester (1 g) in conc. sulphuric acid (3 ml) was heated on a steam-bath for 2 hr. The solution was poured into ice water. The precipitate was collected and recrystallized from methanol-chloroform to give 5-nitro-N-phthaloylhistidine methyl ester (0·7 g), m.p. 301° (d) (Found: C, 49·49; H, 3·75. $C_{15}H_{12}N_4O_6.H_2O$ requires C, 49·73; H, 3·90%).

The foregoing phthalimide (3·2 g) was heated under reflux with conc. hydrochloric acid (20 ml) for 4 hr. The solution was diluted with water and extracted with chloroform. The aqueous solution was evaporated to dryness and the residue crystallized from methanol to give XXV (1·3 g), m.p. 253° (d) (Found: C, 30·67; H, 4·23; N, 24·09. $C_6H_9ClN_4O_4$ requires C, 30·45; H, 3·83; N, 23·68%).

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